SYNOPSIS

Title of the study: A multicenter, double-blind, parallel-group, placebo-controlled study of the effect on cognitive performance and safety/tolerability of SSR180711C, at the doses of 2, 8, and 20 mg/d for 4 weeks, using donepezil as calibrator, in patients with mild Alzheimer's Disease (Study PDY10400).
Investigator(s): Not disclosed
Study center(s): France, Italy, Spain, Sweden
Publications (reference): Not applicable
Study period: Date first patient enrolled: 07 January 2008 Date last patient completed: 10 July 2008
Phase of development: 2
Objectives: The primary objective was to assess the effect of SSR180711C at the doses of 2, 8, and 20 mg/d for 4 weeks, in comparison to placebo, on cognitive performance in patients with mild Alzheimer's Disease (AD). The secondary objectives were to: • explore the effect of SSR180711C on global clinical status, functional impairment and behavioral disturbances in patients with mild AD • assess the safety/tolerability of SSR180711C in patients with mild AD
Methodology: Multicenter, multinational, randomized, double-blind, double-dummy, parallel-group (5 groups), placebo-controlled with a calibrator arm (donepezil)
Number of patients: Planned: 200 Randomized: 1 Treated: 1 Efficacy/pharmacodynamic: NA Safety: 1 Pharmacokinetics: 1

Diagnosis and criteria for inclusion:

***Inclusion*:**

- Outpatients with diagnosis of mild AD based on the Dementia of Alzheimer's type Diagnostic and Statistical Manual for Mental Disorders, 4th edition criteria and the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria for probable AD and supported by a Magnetic Resonance Imaging result consistent with the diagnosis and a modified Hachinski score ≤4.
- Severity established by Mini Mental State Examination (MMSE) ≥20 and ≤26 at screening, and ≥19 and ≤27 at baseline, and Clinical Dementia Rating at 0.5 or 1 at screening.

***Exclusion*:**

- Age <55 years or >90 years
- Concomitant or previous treatment by acetylcholinesterase inhibitors and/or memantine (ie, patients will be "naïve" with respect to these treatments).
- History of epileptic seizures
- Medical condition which may interfere with the study
- Lens opacity, defined by Lens Opacities Classifications System Version III (LOCS III) grading above predefined thresholds and/or surgical treatment scheduled/anticipated in the following months
- Lack of reliable caregiver

Investigational product: SSR180711C

Dose: 2, 8, or 20 mg
Administration: Oral
Batch number(s): Not disclosed

Duration of treatment: 4 weeks

Duration of observation: 6.5 months

Reference therapy: Placebo and Donepezil

Dose: Donepezil 5 mg
Administration: Oral
Batch numbers:
SSR180711 placebo: Not disclosed
Donepezil placebo: Not disclosed
Donepezil: Not disclosed

Criteria for evaluation:

Efficacy:

Primary endpoints:

Cognitive performance, evaluated by the Cognitive Drug Research computerized assessment system (CDR-S)

Secondary endpoints:

Alzheimer's Disease Assessment Scale-Cognitive sub scale score, Alzheimer's Disease Cooperative Study-Activities of Daily Living score

MMSE score, Neuropsychiatric Inventory total score (frequency * severity), Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory

***Safety and tolerability*:**

Adverse events (AEs), physical examinations, vital signs, clinical laboratory tests, electrocardiograms (ECG)s, ophthalmologic examination including slit lamp use with grading on the Lens Opacities Classification System Version III (LOCS III).

Convulsions and worsening of lens opacity are defined as AEs of special interest. All related AEs were to be reported using serious adverse event (SAE) process and immediately reviewed by an independent Data Monitoring Committee (DMC) who had specific expertise in these fields.

The DMC was also to review all SAEs and premature discontinuations.

Statistical methods:

***Statistical considerations*:**

Sample size:

Calculation was based on the available literature on the power of attention test of the CDR-S in AD (1) and Age Associated Memory Impairment (2). Type I error = 5%, power = 80%.

Previously observed effect size was delta=464 ms (standard deviation = 710) leading to a standardized effect size of 0.65. The sample size was based on the test of each SSR180711C dose versus placebo (without adjustment for multiple comparisons).

Forty patients were planned to be included in each arm taking into account an 8% drop out rate.

Primary population of analysis:

The primary population of analysis was to be the population of patients treated, with a baseline and a post-baseline cognitive battery measurement, analyzed in their actual treatment group.

Primary analysis:

Comparison of each dose of SSR180711C versus placebo using an analysis of covariance on the change from baseline to last visit evaluated using the last observation carried forward approach, with treatment as a fixed factor, and including baseline as the covariate. The 95% confidence interval was given. The calibrator arm was to be compared to placebo to measure assay sensitivity.

As an additional analysis, linear regression was also to be used to evaluate a possible dose-effect. The coefficient attached to the dose (slope) was to be tested versus 0. If the data showed departure from linearity, a logarithmic transformation, a quadratic effect, ordinal or other nonlinear models could have been used.

Secondary efficacy endpoints analyses were to be analyzed with the same strategy as the primary criteria.

Safety analysis was to be descriptive.

Summary:

The current report is synoptic-style report, and as such, no results are presented in full.

The study started 07 January 2008 (first and only patient signed informed consent). The study was temporarily halted on 29 February 2008, pending full evaluation of 3 cases of lens opacities observed in Phase 1 studies. The development of SSR180711C in Alzheimer's disease was then discontinued due to insufficient expected benefit/risk profile and the study definitively terminated (the study was prematurely terminated on 24 July 2008 and the study termination decision was communicated to the Investigators by a letter dated 2 September 2008).

Only 1 patient (71-year-old male) was included in study PDY10400. This patient was on 20 mg SSR180711C and had already completed the 4-week study treatment prior to the suspension of enrolment (last study drug administration on 18 February 2008). No AEs were reported. There were no clinically significant ECG and laboratory abnormalities. Ophthalmologic examinations were performed as per protocol, before baseline, and 2-week and 5-month post-treatment, with pupil dilation and quantification using the Lens Opacity Classification System, Version III. No significant changes in scores were observed. The data of this patient are appended in the CSR.

Date of report: 30-Apr-2009